Case report

Journal of the Intensive Care Society
2016, Vol. 17(4) 346–352

DOI: 10.1177/1751143716638371
jics.sagepub.com

Status epilepticus and anti-NMDA receptor encephalitis after resection of an ovarian teratoma

Amritpal S Jandu, Peter M Odor and Steven D Vidgeon

Abstract

Anti-N-methyl-D-aspartate receptor encephalitis is a recently recognised autoimmune, paraneoplastic syndrome that typically presents with psychiatric disturbance, reduced conscious level and seizures. The disorder has been previously associated with ovarian teratomas. We present the case of a 35-year-old female, with a previous surgical history for resection of an ovarian teratoma, who later developed status epilepticus and anti-N-methyl-D-aspartate receptor encephalitis requiring intensive care management. Her presentation, treatment and early follow-up are described, alongside an overview of anti-N-methyl-D-aspartate receptor encephalitis pathophysiology and intensive care management.

Keywords

Encephalitis, status epilepticus, anti-NMDA receptor antibody

Case presentation

A 35-year-old female, with no known prior medical problems, was brought by ambulance to a district general hospital following her first presentation of a short, self-terminating tonic-clonic seizure at home. On arrival to the emergency department, the patient was obtunded, pyrexial but otherwise haemodynamically stable. On examination, Glasgow Coma Score was initially 9 (E3, V1, M5) improving to 14 (E4, V4, M6) within 30 min, with normally reactive pupils and no focal neurological signs nor meningism. The patient had a patent airway, adequate ventilation and SpO_2 of 100% on 10 l/min of oxygen via a non-rebreathe mask. Physiological observations showed a temperature of 38.3°C, a mild sinus tachycardia of 110 beats/min and blood pressure of 110/65 mmHg. She had evidence of urinary incontinence and tongue biting. No skin rashes were visible on secondary survey. Initial investigations including biochemical, haematological, thoracic radiograph, arterial blood gas and ECG were unremarkable. Inflammatory markers showed WBC 7.9 and CRP 11.

Following an early post-ictal phase, the patient's neurological status improved. She was subsequently able to self-report her medical background, which was corroborated by accompanying family members. The patient provided a 2-week history of sore throat and cough, for which her general practitioner had initiated a course of erythromycin. She denied any drug/alcohol abuse, medical or surgical admissions to hospital; there was no prior history of seizures nor neurological disorders, and she had undertaken no recent foreign travel. General and neurological examination were unremarkable.

A further tonic-clonic seizure was witnessed, which failed to response to intravenous lorazepam, and the decision was taken to intubate in the emergency department, prior to transfer for a CT scan of her head. This investigation did not reveal any intracranial abnormality.

On the intensive care unit (ICU), she developed intractable status epilepticus, despite sedation with a propofol infusion. Intravenous phenytoin and levetiracetam were administered to attenuate seizure activity, alongside broad-spectrum antibiotics and intravenous acyclovir to treat possible bacterial meningitis and herpetic encephalitis. Evolution of the patient's condition continued over the first 24 h in hospital, with persistent seizures, requiring escalation

Intensive Care Department, Croydon University Hospital, Croydon, UK

Corresponding author:
Amritpal S Jandu, Intensive Care Department, Croydon University Hospital, 530 London Rd, Croydon, Surrey CR7 7YE, UK.
Email: amritpaljandu@nhs.net

of anti-epileptic dosing and commencement of an infusion of thiopental to effectively terminate convulsive seizures. Four channel EEG monitoring using a bispectral index device (BIS, Covidien) was used to monitor seizure activity and to achieve an isoelectric EEG.

Investigation into the cause of her rapidly progressing condition included early lumbar puncture, which showed a marginally raised glucose, normal protein and leucocyte counts with no organisms seen under microscopy. Serum and cerebrospinal fluid (CSF) samples for viral polymerase chain reaction (PCR) tests for herpes simplex virus (HSV), human immunodeficiency viral (HIV), cytomegalovirus (CMV), Epstein–Bar virus (EBV), Varicella Zoster virus and Enterovirus subsequently returned as negative.

Full multi-channel electroencephalography (EEG) was undertaken once seizures were controlled and showed widespread rhythmical delta activity (a non-specific EEG finding, which can sometimes be correlated with encephalopathy) but no epileptiform discharge. During the EEG investigation, the patient was receiving a propofol infusion and had been administered thiopental 48 h previously, which may have influenced the readings.

Weaning of sedation over subsequent days was limited by partial tonic-clonic seizures, which were managed with long-acting benzodiazepines. With no haemodynamic compromise, minimal respiratory support required and seizures apparently controlled, extubation was able to take place on day 4. However, the patient was agitated, exhibiting severe verbal and physical aggression towards staff and relatives, which required repeat sedation, intubation and commencement of regular anti-psychotic medication.

On day 5 on ICU, further history from family members brought the beginnings of an answer to the patient's diagnostic conundrum: the patient had undergone laparoscopic surgery at a private hospital several years prior to this admission to remove a cyst from her left ovary. After contacting the private hospital, we learnt that the patient's excised cyst was a left-sided ovarian teratoma. A tentative diagnosis of ovarian teratoma associated anti-NMDA receptor encephalitis was considered, and further investigation was undertaken to confirm the pathology.

Urgent transvaginal ultrasound showed a new 4.5 cm × 5 cm cystic lesion, suspected to be dermoid cyst on the right ovary (contralateral to the previously resected ovarian cyst). Serum was sent for anti-NMDA receptor antibody titres and the patient was transferred to a tertiary neurological centre for plasmaphoresis. Rigorous radiological evaluation of the suspected ovarian cyst was subsequently undertaken to determine a possible need for surgical treatment. However, despite CT, MRI and repeat ultrasound examinations, no conclusive evidence could be found to confirm the presence of a teratoma or other tumour. A multi-disciplinary team meeting was convened and concluded that the suspected lesion seen around the right ovary represented fat stranding and that laparoscopic exploration was not indicated as there was no conclusive evidence of a teratoma on repeated scans.

Subsequently, the NMDA-receptor antibody serology returned positive. The patient made a significant neurological recovery in 3 weeks following plasmaphoresis, eventually stepping down from critical care to a neurology ward with a tracheostomy in situ. She achieved a full neurological recovery and the patient was discharged home on sodium valproate with follow-up in neurology clinic. She was subsequently seen in the neurology clinic one month after discharge where a decision was made to wean down the anti-epileptic medication with a view to stopping. The patient however had another emergency department admission 2 months following this, presenting with headaches and visual disturbances. She was reviewed by the neurology team, an unrelated diagnosis of migraines with aura was made and the patient was discharged home the following day. She has not had any further episodes of seizures to date and is under regular follow-up.

Pathophysiology of anti-NMDA receptor encephalitis

Anti-NMDA receptor encephalitis was first characterised by Dalmau et al.[1] This auto-immune, paraneoplastic syndrome is most commonly associated with the finding of ovarian teratoma.[1–3] However, it has also been diagnosed in association with testicular cancer, mediastinal teratomas, small cell lung adenocarcinoma, neuroblastomas, breast cancer and Hodgkin lymphoma.[4]

Not all diagnosed anti-NMDA receptor encephalitis are associated with the presence of a neoplasm; Dalmau et al. reported 40 (41%) of 98 patients in whom NMDA-R encephalitis was confirmed but had no macroscopically identifiable tumour. Of the 58 patients (59%) in whom a tumour was identified, 56 (97%) were female and 2 (3%) were male. Of those 56 females in whom a tumour was identified, 53 (95%) had an ovarian teratoma.[1]

Teratomas tumours of germ cell origin are commonly composed of multiple cell types derived from one or more of the three embryonic germ layers (ectoderm, mesoderm and endoderm). Teratomas range from benign, well-differentiated cystic lesions (also known as a dermoid cyst) to those that are solid and malignant. Because they arise from totipotential cells, they are encountered commonly in the gonads (29%). By far, the most common gonadal location is the ovary, although they also occur somewhat less frequently in the testes. Cells differentiate along various germ lines, essentially transforming into any tissue of the body including hair, teeth, fat, skin,

muscle, endocrine tissue and tissue resembling the central nervous system.[5,6]

Microscopic analysis of the ovarian teratomas in the case series by Dalmau et al. confirmed the presence of central nervous tissue. Twenty-five samples of the tumour were further analysed microscopically to confirm the presence of NMDA receptors and all yielded positive results.[1] NMDA receptors are ligand-gated cation channels, which play a role in synaptic transmission, plasticity, memory and learning in the CNS. The receptors are heteromers of NR1 subunits that bind glycine and NR2 subunits that bind glutamate, respectively.

Anti-NMDA receptor encephalitis is an immune-mediated syndrome whereby autoantibodies are produced against NMDA receptors present in neurological tissue found in teratomas. These autoantibodies cross react with NMDA receptors located in the central nervous system.[1–3,7] NR1 and NR2 heteromers predominate within the hippocampus, with less intense reactivity described in the forebrain, basal ganglia, spinal cord and cerebellum. Hence, antibodies may preferentially affect areas responsible for memory, personality, movement and autonomic control, accounting for the range of symptoms seen in this disease process – personality changes, impairments in cognition, motor derangements, bradyarrhythmias and disturbances in respiratory drive.[8,9]

The presence of an underlying tumour varies with age, sex and ethnic background. An analysis carried out of 400 patients with anti-NMDA receptor encephalitis indicated that a tumour is more likely to be confirmed in women aged over 18 and is slightly more predominant in non-Caucasian women.[1,10] A multicentre, population-based prospective study of causes of encephalitis in the United Kingdom, which investigated 203 patients, reported 4% as having anti-NMDA receptor encephalitis.[11] In another retrospective analysis of encephalitis of unknown origin, anti-NMDA receptor antibodies were identified in 1% of patients (aged between 18 and 35 years) admitted to an ICU in Germany.[12] Eighty percent of those diagnosed were female.[1,12]

There is a correlation between antibody titres in the CSF (and to a lesser extent serum) and clinical outcomes, with higher titres associated with increased severity of disease and more protracted recovery. Gurres-Arribas et al. examined 35 paired serum and CSF samples of patients with confirmed anti-NMDA receptor encephalitis. The samples were taken at three different time intervals. The first samples were obtained at the time of diagnosis (median 0.9 month from symptom onset, second obtained after a median follow-up of 3.6 months and the third at the last follow-up (median 12.5 months)).[13] A multivariable analysis in this study showed significantly higher antibody titres in patients with poor-outcome compared with those with good-outcome. Good outcome was defined as Modified Rankin Score[13,14] (mRS) of 0–2 points, and poor outcome as $mRS > 2$.[13]

Analysis of the follow-up of serum and CSF titres not at a group level, but in individual patients, showed a substantial decrease of titres between the first and second time points in the CSF of 12/21 (57%) cases with good outcome, while this only occurred in 3/10 (30%) cases with poor outcome.[13] Higher titres are also found in patients with confirmed malignancies.[7,13,15] This is coupled to the findings of a decrease in the number of postsynaptic clusters of NMDA receptors with the presence of antibodies. This latter effect can be reversed in vivo by removing antibodies from cultures. The reversibility of neurological symptoms suggests that this is immunologically mediated neuronal dysfunction as opposed to an irreversible degeneration.[7]

Hughes et al. established with in vivo experimentation that antibodies mediate the loss of surface NMDA receptors in part by binding to, capping and cross-linking NMDA receptors, resulting in their internalisation.[15] Further evidence to suggest that antibodies are involved in the down regulation of NMDA receptors can be demonstrated by the use of NMDA-receptor antagonists such as ketamine and phencyclidine, which can cause symptoms similar to anti-NMDA-receptor encephalitis, including psychotic behaviour, signs of involvement of dopaminergic pathways (rigidity, dystonia, orofacial movements, tremor) and autonomic dysfunction.[7,15]

Antibodies in the CSF are consistently found in higher concentrations as opposed to the serum. The origin of the antibodies – whether formed within the CSF or externally in the serum is still debated.[15] One potential mechanism is the production of autoantibodies in the serum which then gain access via the blood–brain barrier (BBB) into the CNS. This however would suggest that there is a breach in the integrity of the BBB to allow passive diffusion of larger molecules, which would not otherwise occur. Proposed mechanisms of this include acute inflammation of the neuronal tissue, which may possibly correlate with the viral prodrome symptoms often seen in the early stages of the disease.[1]

Rabchecvksy et al. demonstrated that Freud's adjuvant, a solution containing heat-inactivated Mycobacterium, is able to provoke peripheral inflammation without adversely affecting the CNS and lead to increased BBB permeability. In vivo experimentation demonstrated progressive increases in the perivascular extravasation of serum IgG, albumin and IgM. Similarly, corticotropin releasing hormone released in acute stress has been shown to facilitate BBB penetration. Thus, it is proposed that systemic inflammation can disrupt the integrity of the BBB, initiating the sequence of events described.[16]

The second mechanism proposed is the production of antibodies in the CNS itself. Evidence for this mechanism is based on a number of findings.

Dalmau et al. demonstrated a preserved BBB in 53 out of 58 patients with anti-NMDA receptor encephalitis. Normalised concentrations of IgG showed that all 53 patients had higher concentrations of antibodies in CSF than in sera, supporting the hypothesis of intrathecal synthesis of antibodies. If there was BBB dysfunction resulting in passive diffusion of IgG, one would have expected normalised concentrations of antibodies to equilibrate between the sera and CSF.[1,7]

It is conceivable that this presentation of anti-NMDA receptor encephalitis was coincidently unrelated to the initial tumour disease. This case has implications for understanding of the disease, since patients may still be at a low risk of anti-NMDA receptor encephalitis, even after removal of a potential precipitant tumour.

In summary, a serologically confirmed diagnosis of anti-NMDA receptor encephalitis was made in a patient who had a previously resected ovarian teratoma. We speculate that three possible mechanisms may explain the development of disease in this individual. First of all that the anti-NMDA receptor antibodies present in this patient could have formed against the left ovarian teratoma she had removed 4 years earlier but remained quiescent in the system. They may gained access to the CNS at a later stage and precipitated the anti-NMDA receptor encephalitis that she was diagnosed with on this presentation. Second, a microscopic tumour recurrence, not identifiable on imaging modalities, may have triggered antibody formation. Third, it is possible that her presentation was unrelated to her initial disease.

At the time the left ovarian teratoma was removed, the patient did not have any of the symptoms associated with this encephalitis. This may possibly have been because the teratoma was removed before the antibodies could instigate the disease process, combined with the fact that the number of antibodies would have been depleted after tumour removal. Conversely, it may simply imply that they were not present at the time.

Recognition and diagnosis of anti-NMDA receptor encephalitis

The initial presentation of anti-NMDA receptor encephalitis is often associated with a viral prodrome (e.g. URTI, diarrhoea, fever, nausea and vomiting) in 70% of cases.[17] Within 2 weeks, this subsequently progresses to psychiatric symptoms (including agitation, insomnia, anxiety, psychosis, hallucinations, memory loss and personality change). Deterioration of language is also commonly observed.[18,19] Psychiatric symptoms tend to manifest early, followed by movement disorders. These include dyskinesia – particularly oro-facial, limb and trunk choreoathetosis, oculogyric crisis, dystonia, rigidity, opisthotonic postures and ataxia. Autonomic dysfunction (cardiac dysrhythmia, tachycardia, bradycardia hyper/hypotension, urinary incontinence, hypersalivation), decreased conscious levels and seizures (including motor and complex) also frequently occur.[3,7]

The overlap of abnormal movements and epileptic seizures can lead to under-recognition of the seizures or unnecessary escalation of antiepiletics for dyskinesias that are interpreted as seizures. Seizure activity is often not detected on EEG and anti-epileptics should be used with caution as they can exacerbate movement disorders.[2,20] For these reasons, patients may be mistaken as having a psychiatric illness and referred to mental health services on initial presentation.[18]

CT brain is most commonly performed in the early stages of presentation to exclude any intra- or extracranial masses or haemorrhage as the cause of symptoms, but does not show any abnormality in this condition. MRI scans of the brain can be normal in 50% of cases. T2 or FLAIR signal hyperintensity can be observed in the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem, and, infrequently, the spinal cord. These changes are often mild and transient and not visible on follow-up scans. There may also be localised contrast enhancement in the surrounding meninges.[1]

CSF is initially normal in 80% of patients but becomes abnormal in later stages of the disease. Moderate lymphocytoticpleocytosis and normal or mildly increased protein and normal glucose can be seen. In the absence of any viral or bacterial cause for encephalitis – gram staining, culture and PCR viral screen are negative. Sixty percent of patients have CSF specific oligoclonal bands present.[3,21] Malter et al. demonstrated that the presence of oligoclonal bands in the CSF increases the likelihood of an underlying autoimmune encephalitis by 8.5 fold and it can further increase the likelihood of an underlying NMDA receptor encephalitis by 16 fold if there are also signs and symptoms clinically correlating to the disease process.[21]

EEG findings usually show non-specific slow, disorganised activity sometimes with evidence of seizures. Slow, continuous, rhythmic activity in the delta-theta range can predominate; however, it is not associated with abnormal movements and does not respond to antiepileptic drugs. Results need to be interpreted with caution however as patients who are intubated and sedated are likely to have non-specific changes and seizure activity will be dampened particularly in the presence of thiopental.[2]

Schmitt et al. reviewed EEG data of 23 hospitalised adult patients with anti-NMDA receptor encephalitis. Seven of 23 patients (30.4%) had a unique electrographic signature, which they termed ‘extreme delta brush’. This involves frontally maximal high-voltage beta activity superimposed on frontally maximal delta waves. The presence of extreme delta brush was associated with a more prolonged hospitalisation and

worse outcomes for patients.[22] This EEG pattern was also noted by Vanhaerents et al. in a young woman with NMDA receptor encephalitis in association with an ovarian tumour. This patient also had persistent symptoms despite surgical resection of the tumour, IV steroids, plasmaphoresis, cyclophosphamide and rituximab 17 weeks post diagnosis.[23]

Investigation for an underlying malignancy is key and the choice of modality will depend on the suspected origin. Certainly with ovarian teratomas transvaginal ultrasound, CT and MRI scans can all be of use, however PET scans maybe beneficial for other suspected tumours such as lymphoma and lung cancer.[24] Of note, it has been documented in case reports that patients who have a slow, protracted recovery with no tumour identifiable on initial presentation, often have ovarian teratomas visible on MRI years after their initial onset of symptoms.[25] Hence, it has been suggested that these patients have regular MRI pelvis surveillance imaging as follow-up.[2–4,7,26]

Critical care implications in anti-NMDA receptor encephalitis

Early involvement of Critical Care may be necessary for any patient with a severe acute neurological condition such as that described. Critical care management is largely supportive whilst investigation and treatment of the underlying condition take place.

Patients with acute confusional or psychotic states of organic origin may be optimally managed in the Critical Care environment, where intensive nursing and the ability to closely monitor the effects of sedation contribute to safe management.

Where the condition itself or the sedative agents used to treat it, lead to a depressed level of consciousness, formal airway protection and management on the Critical Care Unit are clearly essential.

As discussed previously, this condition may respond poorly to conventional anti-epileptic treatment. In patients with intractable seizures it is essential to rapidly terminate seizure activity to prevent hypoxic neurological injury using propofol, or failing that barbiturates (e.g. an infusion of thiopental).

Formal EEG and regular clinical neurological assessment are an essential part of the investigation of any patient with intractable seizures and may be rendered un-interpretable in the presence of long acting barbiturates such as thiopental. Therefore, these drugs should be reserved as a last resort and agents with short context sensitive half-times like propofol and remifentanil should be used in preference. If there is significant rhabdomyolysis and hence acute kidney injury, it may be necessary to institute renal replacement therapy.

Continuous formal EEG monitoring maybe desirable; however, it is rarely available outside of specialist neurological intensive care units and even then requires specialist interpretation. In our case, we found the use of four-channel EEG monitoring (BIS, Covidien), displaying the raw EEG signal, invaluable as a tool to detect sub-clinical seizures and to titrate and monitor the effects of anti-epileptic agents.

It is important to initially treat and exclude common global neurological conditions, which may result in a similar presentation, for example, acute meningitis or encephalitis of infective origin. Failure to respond to conventional treatment and unremarkable routine investigations should alert the clinician to the possibility of an underlying paraneoplastic syndrome, particularly in young female patients.

Specialist neurological advice is essential in guiding anti-convulsant treatment and specific investigations for those unfamiliar with the condition. Attempts at withdrawal/reduction in sedative agents are unlikely to be successful, whilst the underlying cause of seizures remains to be addressed.

Treatment for anti-NMDA receptor encephalitis

The mainstay of treatment for NMDA receptor encephalitis is immunotherapy and tumour resection. Immunotherapy is often divided between first line agents (IV steroids, immunoglobulins and plasma exchange) and second line immunomodulative agents (Rituximab and cyclophosphamide).[2,3,7,27]

Titulaer et al. investigated the treatment effects and outcomes in 501 patients with NMDA encephalitis who were followed up for 24 months. From this cohort, 472 (92%) patients received first line immunotherapy and tumour resection where applicable; 251/472 (53%) showed symptom improvement in 4 weeks. During the first 24 months, 241/251 reached a mRS 0-2 (median 3 months) and at 24-month follow-up 111/115 (97%) of these patients had scores 0–2 on the modified Rankin Scale.[26] Of the 472 patients who received first line immunotherapy and tumour resection where applicable, 221/472 (47%) continued with poor mRS scores (median 5). A total of 125 of these patients (57%) went on to receive second-line immunotherapy and 96 (43%) had no further immunotherapy or continued receiving first-line immunotherapy.[26]

When comparing this cohort of 125 patients escalated to second line immunotherapy, 84/125 (67%) reached a mRS 0–2 during the first 24 months (median 10 months). However, in the 96 patient who did not receive second line immunotherapy, 49/96 (51%) reached an mRS 0–2 (median 15 months) during the first 24 months.[26] Hence, patients who did not respond to first line treatment at 4 weeks improved clinically on second line treatment of rituximab, cyclophosphamide or both. They had better outcomes compared with those who continued with first-line immunotherapy (or received no

further immunotherapy). However, the results also indicate that even with no further intervention after first line treatment, many patients do improve spontaneously.

Predictors of good clinical outcomes, as defined by reductions in modified Rankin scores, include lower severity of symptoms assessed as no need for ICU support; lower levels of antibodies, early (<40 days) administration of immunotherapies in non-paraneoplastic patients and earlier tumour removal in paraneoplastic patients.[26,28] A better prognosis is also associated with NMDA receptor encephalitis where an identifiable tumour is present compared with those in whom a malignancy is not present.[1]

Mortality from case series is reported as ranging between 4 and 10%.[10] Relapses have been reported in 20–25% of patients by Dalmau et al. who investigated 100 patients and 12% by Titulaer et al.[26,29] Titulaer et al. reported 45/501 12% of patients had clinical relapses in their 24 month follow-up. In all, 15/45 patients (33%) had multiple relapses.[26] However, compared with the initial episode, 46/69 (67%) of the relapses were less severe (as reflected by a lower mRS score measured at the stage of maximum severity), more frequently mono-symptomatic (24, 35%), and resulted in fewer admissions (12, 17%) to the ICU.[26]

Those in whom a malignancy was identified and also received concomitant immunotherapy treatment had a lower rate of relapse. Patients without a tumour had a higher frequency of relapses than those with a tumour.[26]

Conclusion

NMDA-receptor encephalitis is a rare and often misdiagnosed disease. Only formally recognised in 2007, it is frequently associated with an underlying neoplasm. We believe this is the first case report in which anti-NMDA receptor encephalitis has developed in a previously asymptomatic individual with a history of ovarian teratoma resection and in the absence of a macroscopically identifiable tumour recurrence.

The symptoms vary as the disease progresses from viral prodrome and psychiatric symptoms to autonomic dysfunction, movement disorders and seizures. There should be a high index of suspicion in women presenting with encephalitis in whom the lumbar puncture does not demonstrate a bacterial or viral origin.

Critical Care management focuses on supportive treatment and aggressive seizure management, whilst efforts are directed to identify an underlying neoplasm early. Early tumour removal and initiation of immunotherapy is key to improved clinical outcomes. If no tumour is identified on presentation, patients may benefit from follow-up surveillance.

Acknowledgement

The patient gave written informed consent for publication of this case report.

Declaration of conflicting interests

The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008; 7: 1091–1098.
2. Florance NR, Davis RL, Lam C, et al. Anti–N-Methyl-D-Aspartate Receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 2009; 66: 11–18.
3. Mann A, Machado NM, Liu N, et al. A multidisciplinary approach to the treatment of anti-NMDA-receptor antibody encephalitis: A case and review of the literature. *J Neuropsychiatry Clin Neurosci* 2012; 24: 247–254.
4. Rosenfeld MR, and Dalmau J. Anti–NMDA-receptor encephalitis and other synaptic autoimmune disorders. *Curr Treat Options Neurol* 2011; 13: 324–332.
5. Kumar V, Abbas AK, and Fausto N. *Robbins and Cotran pathologic basis of disease* (7th ed.). Philadelphia: Elsevier Saunders, 2005.
6. Grosfeld JL, and Billmire DF. Teratomas in infancy and childhood. *Curr Probl Cancer* 1985; 9: 1–53.
7. Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011; 10: 63–74.
8. Day GS, High S, Cot B, et al. Anti-NMDA-receptor encephalitis: Case report and literature review of an under-recognized condition. *J Gen Int Med* 2011; 26: 811–816.
9. Newcomer JW, Farber NB, and Olney JW. NMDA receptor function, memory and brain aging. *Dialogues Clin Neurosci* 2000; 2: 219–232.
10. Gable MS, Gavali S, Radner A, et al. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. *Eur J Clin Microbiol Infect Dis* 2009; 28: 1421–1429.
11. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis* 2010; 10: 835–844.
12. Prüss H, Dalmau J, Harms L, et al. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. *Neurology* 2010; 75: 1735–1739.
13. Gresa-Arribas N, Titulaer MJ, Torrents A, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol* 2014; 13: 167–177.
14. Banks JL, and Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for

stroke clinical trials: a literature review and synthesis. *Stroke* 2007; 38: 1091–1096.
15. Hughes EG, Peng X, Gleichman AJ, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J Neurosci* 2010; 30: 5866–5875.
16. Rabchevsky AG, Degos JD, and Dreyfus PA. Peripheral injections of Freund's adjuvant in mice provoke leakage of serum proteins through the blood-brain barrier without inducing reactive gliosis. *Brain Res* 1999; 832: 84–96.
17. Peery HE, Day GS, Dunn S, et al. Anti-NMDA receptor encephalitis. The disorder, the diagnosis and the immunobiology. *Autoimmun Rev* 2012; 11: 863–872.
18. Wandinger KP, Saschenbrecker S, Stoecker W, et al. Anti-NMDA-receptor encephalitis: a severe, multistage, treatable disorder presenting with psychosis. *J Neuroimmunol* 2011; 231: 86–91.
19. Kleyensteuber B, Ruterbusch V, Bennett J, et al. Limbic encephalitis presenting with seizures, anterograde amnesia, and psychosis in a patient seven weeks status post-immature ovarian teratoma removal. *Mil Med* 2010; 175: 616–618.
20. Chapman MR, and Vause HE. Anti-NMDA receptor encephalitis: Diagnosis, psychiatric presentation, and treatment. *Am J Psych* 2011; 168: 245–251.
21. Malter MP, Elger CE, and Surges R. Diagnostic value of CSF findings in antibody-associated limbic and anti-NMDAR-encephalitis. *Seizure* 2013; 22: 136–140.
22. Schmitt SE, Pargeon K, Frechette ES, et al. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* 2012; 79: 1094–1100.
23. VanHaerents S, Stillman A, Inoa V, et al. Early and persistent 'extreme delta brush' in a patient with anti-NMDA receptor encephalitis. *Epil Behav Case Reports* 2014; 2: 67–70.
24. Taylor MB, Bromham NR, and Arnold SE. Carcinoma of unknown primary: key radiological issues from the recent National Institute for Health and Clinical Excellence guidelines. *Br J Radiol* 2012; 85: 661–671.
25. Iizuka T, Yoshii S, Kan S, et al. Reversible brain atrophy in anti-NMDA receptor encephalitis: a long-term observational study. *J Neurol* 2010; 257: 1686–1691.
26. Titulaer MJ, Soffietti R, Dalmau J, et al. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. *Eur J Neurol* 2011; 18: 19-e3.
27. Ishiura H, Matsuda S, Higashihara M, et al. Response of anti-NMDA receptor encephalitis without tumour to immunotherapy including rituximab. *Neurology* 2008; 71: 1921–1923.
28. Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain* 2010; 133: 1655–1667.
29. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* 2013; 12: 157–165.